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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
09/628,495	07/28/2000	David White	MPI99-130PTRM	3801

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EXAMINER
NICHOLS, CHRISTOPHER J

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 03/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/628,495	WHITE, DAVID	
	Examiner	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 January 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *73-85* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *73-85* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 September 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7, 11,16* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Application, Amendments, And/Or Claims

1. The amendments filed 30 September 2002 (Paper No. 19), 13 January 2003 (Paper No. 20), 13 January 2003 (Paper No. 21), and 13 January 2003 (Paper No. 22) have been entered in full. Claims 25-31, 37-38, and 51-72 have been cancelled and claims 73-85 have been added. Claims 73-85 are under examination.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections And/Or Rejections

3. The objections to the specification regarding the title and informalities as set forth at pp. 2-3 ¶ 4-5 of the previous Office Action (Paper No. 18, 13 September 2002) is *withdrawn* in view of Applicant's amendments (Paper No. 22, 13 January 2003).

4. All previous objections to and rejections of claims 25-31, 37, 38, and 51-72 are withdrawn in view of the cancelled claims.

Maintained Objections And/Or Rejections

5. Claims 73-85 are rejected under 35 U.S.C. 112 ¶ 1 as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons as set forth in at pp. 3-9 ¶ 6-16 of the previous Office Action (Paper No. 18, 13 September 2002). It is noted that the Applicant has cancelled claims

25-31, 37-38, and 42-72 and added claims 73-85. Therefore, the rejection of claim 25-31, 37-38, and 42-72 is applied to the newly added claims, 73-85.

6. The Applicant traverses the 35 USC 112 ¶ 1 rejection of claims 25-31, 37-38, and 42-72 as set forth in at 3-9 ¶ 6-16 of the previous Office Action (Paper No. 18, 13 September 2002) on the grounds that the specification and the prior art are sufficient to enable one of ordinary skill in the art to make and/or use the instant invention. The Applicant notes the Examiner's acknowledgement of guidance for an *in vitro* system (pp. 17, "**Rejection of the claims under 35 U.S.C. § 112, first paragraph**", Paper No. 22, 13 January 2003).

7. Applicant's arguments have been fully considered but are not deemed to be persuasive for the following reasons. Regarding the specification's teachings concerning using MRR (melatonin-related receptor; SEQ ID NO: 1 for the instant application) as a diagnostic for a bone disease, the specification and prior art teach the use of an *in vitro* system to assay for the binding of a compound to MRR. However, it is not clear from the prior art or the specification as to what constitutes an agent that modulates "...a MRR mediated bone-related disorder". Due to the large quantity of experimentation necessary to identify an agent involved in "modulating a MRR mediated bone-related disorder", the lack of direction/guidance presented in the specification regarding compounds involved in "modulating a MRR mediated bone-related disorder", the absence of working examples directed to compounds involved in "modulating a MRR mediated bone-related disorder", the complex nature of the invention, and the breadth of the claims which fail to recite limitations compound with MRR mediate bone-related disorder modulating

activity, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

8. Concerning the Examiner's Acknowledgement at pp. 4 of the previous Office Action (Paper No. 18, 13 September 2002) where the Examiner states "general guidance is provide regarding preparing an *in vitro* system to execute the invention". This should not be misconstrued to mean that the invention is enabled, only that general guidance concerning using an *in vitro* assay to detect compounds which bind to a given protein, a MRR protein in this case, in a biological sample is provided. Note, this procedure is routine and not disputed, the existence of a relationship between MRR and bone diseases are what is called into question by the previous Office Action (Paper No. 18, 13 September 2002).

9. The Applicant also traverses the 35 USC 112 ¶ 1 rejection of claims 25-31, 37-38, and 42-72 as set forth in at 3-9 ¶ 6-16 of the previous Office Action (Paper No. 18, 13 September 2002) on the grounds that the present rejection does not meet the requirement of the USPTO to establish a reasonable uncertainty of enablement in order to maintain such a rejection (M.P.E.P. 2164). The Applicant alleges that the specification demonstrates a nexus between MRR and bone formation thus the usefulness of identifying compounds for the treatment of bone disorders is implicit. The Applicant further alleges that the instant specification also provides support for bone–related disorders and the function of MRR in said disorders. The Applicant maintains that Figure 3 and 4 of the instant applicant provide evidence for the involvement of MRR in bone-related disorders. It is alleged that the expression of MRR at E18.5 in murine embryonic limb bone precursors and vertebral disk hone precursors would lead one of ordinary skill

in the art to conclude that MRR is involved in bone-related disorders (pp. 18, "**Rejection of the claims under 35 U.S.C. § 112, first paragraph**", Paper No. 22, 13 January 2003).

10. Applicant's arguments have been fully considered but are not deemed to be persuasive for the following reasons. Concerning the present rejection not meeting the requirements for a proper rejection, the Previous Office action (Paper No. 18, 13 September 2002) only acknowledged general guidance concerning using an *in vitro* assay to detect compounds which bind to a given protein, a MRR protein in this case, in a biological sample is provided. Note, this procedure is routine and not disputed, the existence of a relationship between MRR and bone diseases are what is called into question by the previous Office Action (Paper No. 18, 13 September 2002). Furthermore, the Previous Office action (Paper No. 18, 13 September 2002) was in fact an enablement rejection noting that the general procedure was not enabled for the use of the method for identifying compounds that modulate a MRR mediated bone-related disorder. This rejection was made on the grounds that: (1) The Applicant failed to provide evidence that MRR was involved in any bone-related disorder, (2) No guidance was given to evaluate the nature or composition of a MRR modulating compound, (3) No MRR bone-related disorder was shown to exist, (4) The nature of the "bone-related disorders" was not presented to a clear and convincing manner such as to enable a person of ordinary skill to practice the invention, (5) No evidence of MRR modulatory compounds as having an alleviating or salubrious effect on bone-related disorders. While MRR may be involved in bone formation, there is no evidence or reason to expect that MRR is mis-regulated in any bone disorders such that it is a viable target to develop drugs. Also, there is no

evidence or reason to expect that MRR is involved in a rate-determining step in bone formation.

11. Concerning the expression of MRR in embryonic bone tissue and the supposition that this is indicative of MRR involvement in bone-related disorders. The art cited by the Applicant in support of the instant specification teaches the contrary. Gubitz and Reppert [(15 January 1999) "Assignment of the Melatonin-Related Receptor to Human Chromosome X (*GPR50*) and Mouse Chromosome X (*Gpr50*)." Genomics 55(2): 248-251(**IDS**)] teaches the cloning of a novel G-protein coupled receptor related to the melatonin receptor designated at H9 also called a Melatonin-Related Receptor (MRR). This MRR is not indicated in any bone-related disorder; in fact, Gubitz and Reppert teach that the loci of the MRR gene in question "...might be relevant to genetically based neuroendocrine disorders." (Abstract)(**IDS**) In respect to expression of MRR genes in bone tissue, Weaver and Reppert [(1996) "The Mel_{1a} melatonin receptor gene is expressed in human suprachiasmatic nuclei." NeuroReport 8: 109-112] teaches that three GPCR melatonin receptor subtypes and a melatonin related-receptor (H9) have been identified in vertebrates (pp. 109). The melatonin-related receptor H9 was shown to be found in the suprachiasmatic nuclei (human tissue sections), a brain structure in vertebrates involved in controlling circadian cycles (Figures 1-3). In addition, De Rienzo et al. [(2001) "Expression of MT1 and Melatonin Related Receptor (H9) in Adult Rat Testis." Perspective in Comparative Endocrinology 1075-1079] teaches that a melatonin-related receptor (H9) was cloned and characterized in the mammalian pituitary. In addition, the melatonin-related receptor (H9) is most closely related to the melatonin receptor family, a receptor family involved in the hypothalamic-pituitary-gonadal axis

that controls circadian and reproductive cycles in mammals (pp. 1076). De Rienzo et al. also teaches that the melatonin-related receptor is expressed in adult rat testis and brain (Figure 1). Taken together, based on sequence homology and expression patterns, these references would lead to the logical conclusion that a melatonin-related receptor would be involved in the modulation of circadian and reproductive cycles not bone-related disorders.

12. The Applicant further traverses the 35 USC 112 ¶ 1 rejection of claims 25-31, 37-38, and 42-72 as set forth in at 3-9 ¶ 6-16 of the previous Office Action (Paper No. 18, 13 September 2002) on the grounds that MRR (SEQ ID NO: 1) is a GPCR as evident from Conway et al. [(7 July 2000) "Chimeric Melatonin mt_1 and Melatonin-Related Receptors: Identification of Domains and Residues Participating in Ligand Binding and Receptor Activation of the Melatonin mt_1 receptor." Journal of Biological Chemistry 275(27): 20602-20609 (**IDS**)] and Reppert et al. (1996) "Cloning of a melatonin-related receptor from human pituitary." FEBS Letters 386(2-3): 219-224 (**IDS**)]. These references teach methods useful for cloning, expression, and ligand binding studies. The Applicant concludes their traversal that the new claims 73-85 are directed to a screening method in which test compound binding to MRR is determined, these compounds are candidates for treatment of bone-related disorders (pp. 19, "**Rejection of the claims under 35 U.S.C. § 112, first paragraph**", Paper No. 22, 13 January 2003).

13. Applicant's arguments have been fully considered but are not deemed to be persuasive for the following reasons. Regarding MRR (SEQ ID NO: 1) as a GPCR, Drew et al. [(1998) "The Ovine Melatonin-Related Receptor: Cloning and Preliminary Distribution and Binding Studies." Journal of Endocrinology 10: 651-661 (**IDS**)] teaches

the cloning of an ovine melatonin-related receptor, a mammalian homolog of the human MRR of the instant application. This MRR was found to be expressed in the hypothalamus, pituitary, retina, and retinal pigment epithelium (RPE) (Figure 7-9). No ligand was successfully identified by Drew et al. (**IDS**) for the new melatonin-related receptor. Drew et al. (**IDS**) also noted that: "Further work will be necessary to determine the possibility of autocrine or paracrine synthesis of a ligand for the ovine melatonin-related receptor in the pituitary or retina. A putative role for the ovine melatonin-related receptor in control and regulation of endocrine function and retinal physiology is suggested by its tissue distribution." (pp. 655, 657) In view of Drew et al. (**IDS**) a person of ordinary skill in the art would have no motivation or reasonable expectation of success in making or use the claimed invention as a means to (1) identify compounds that modulate MRR, (2) identify MRR modulating compounds participating in bone-related disorders, or (3) any MRR modulating compound have an affect on a bone-related disorder.

14. Concerning Conway et al. (**IDS**) and Reppert et al. (**IDS**), the Examiner does not question whether or not said references successfully teach the cloning, expression, and ligand binding studies of a melatonin-related receptor. In addition, the Examiner does not question whether or not SEQ ID NO: 1 is in fact a GPCR or a MRR, the Examiner maintains the rejection of the pending claims on the grounds that the said claims encompass identifying candidate compounds for treatment of a "MRR mediated bone-related disorder." While the Examiner does not doubt the usefulness of Conway et al. (**IDS**) and Reppert et al. (**IDS**) in terms of cloning, expression, and ligand binding studies of a novel melatonin-related receptor GPCR, the Examiner maintains that the said

references are silent, and therefore of no relevance, to compounds that modulate a "MRR mediate bone-related disorder." Further said references are also silent on the role of the cloned melatonin-related receptor in terms of its role in bone-related disorders. In fact, Reppert et al. (**IDS**) teaches that the MRR (H9 or melatonin-related receptor) is a member of the melatonin receptor family (Figure 3) and is expressed in human pituitary and hypothalamus (Figure 4). Reppert et al. (**IDS**) explicitly states: "The expression of H9 mRNA in human hypothalamus and pituitary suggests that the receptor and its ligand are involved in the regulation of neuroendocrine function."(pp. 224) Therefore, the silence of Conway et al. (**IDS**) and the teaching of Reppert et al. (**IDS**) in conjunction with the other art cited above, would lead a person of ordinary skill in the art to conclude that MRR has a role in neuroendocrine regulation. In addition, none of the references cited by the Applicant or the Examiner conclusively teach a ligand, natural or otherwise for MRR. The preponderance of evidence presented by the prior art teaches a contrary conclusion to the instant specification thus yielding a situation of uncertainty and unpredictability for use of MRR to screen for candidates for a bone-related disorder.

15. Finally, the Applicant's argument has been taken into full consideration and is not found persuasive. The Applicant has failed to show any convincing evidence in the prior art or specification of a relationship between MRR and any bone disease.

Therefore, the rejection of claims 73-85 under 35 USC 112 ¶1 is maintained.

Summary

16. No claims are allowed.

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher J. Nichols whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:30AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Signature of Examiner

CJN
March 4th, 2003